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*Published in:*  
Cerebral Cortex

*DOI:*  
[10.1093/cercor/bhr124](https://doi.org/10.1093/cercor/bhr124)

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*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2012

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Curcic-Blake, B., Swart, M., & Aleman, A. (2012). Bidirectional Information Flow in Frontoamygdalar Circuits in Humans: A Dynamic Causal Modeling Study of Emotional Associative Learning. *Cerebral Cortex*, 22(2), 436-445. <https://doi.org/10.1093/cercor/bhr124>

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# Bidirectional Information Flow in Frontoamygdalar Circuits in Humans: A Dynamic Causal Modeling Study of Emotional Associative Learning

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**Everyday language is replete with descriptions of emotional events that people have experienced and wish to share with others. Such descriptions presumably rely on pairings of affective words and visual information (such as events and pictures) that have been learnt throughout one's development. To study this kind of affective language learning in the brain, we used functional neuroimaging during associative learning of emotional words and pictures. Brain imaging revealed increased activation of both primary emotional areas such as the amygdala and of higher cognitive areas such as the inferior frontal gyrus (IFG) and medial frontal gyrus. The dynamic causal modeling with Bayesian model selection suggested that the IFG first receives the input and that the connections are bidirectional, suggesting that during such emotional picture–word pair learning, the frontal cortex drives the amygdala activation. Specifically, the interaction between the frontal regions and the amygdala was enhanced by active learning involving both negative and positive emotional stimuli as compared with neutral stimuli. This circuit (especially for negative stimuli) converges with emotion regulation circuits. The enhancement in the connectivity might be responsible for the emotional memory effect in this type of learning.**

**Keywords:** associative learning, DCM, emotional learning, language learning, word–picture association

## Introduction

Associative learning of verbal and visual information, for example coupling words to emotional scenes and situations, is key for the development of healthy emotion regulation in humans. In the process of learning language, a toddler must learn associations between words and their referents (such as objects, verbs, and abstract things such as feelings). A child's lexical development starts by learning how words are used in regulating social interactions, thereby affecting the behavior of others (Karmiloff and Karmiloff-Smith 2002). For that, the associative learning of emotional visual referents (e.g., pictures) and verbal categories (words) might be of particular relevance. During development, associative emotional visual and verbal learning also helps in the acquisition of effective emotion regulation skills (Lane and Nadel 2000; Aleman 2005; Eisenberg et al. 2005). This is important, for example, in order to control and attenuate primitive emotional responses as was highlighted in studies of emotion regulation by affect labeling (Hariri et al. 2000; Banks et al. 2007; Delgado et al. 2008). Both verbal emotional deficiencies and abnormalities in emotional learning are often observed in psychiatric disorders such as schizophrenia (Aleman and Kahn 2005), autism (Happé and Frith 1996), bipolar disorder (Phillips et al. 2003), depression (Heller et al.

1995; Phillips et al. 2003), and posttraumatic stress disorder (Banich et al. 2009). However, nothing is known regarding the neural circuits involved in actual emotional associative learning of verbal and visual information.

Previous research has concentrated on either emotional learning only or associative learning only. Many studies have demonstrated that emotions enhance learning (Richter-Levin 2004; Phelps 2004; Phelps and LeDoux 2005; Phelps 2006; LaBar and Cabeza 2006; Kensinger 2009) such that, for example, emotional experiences are better remembered than neutral experiences (Cahill and McGaugh 1998). The memorizing of emotional and neutral words is improved when they are presented in an emotional context (Brierley et al. 2007). During emotionally arousing learning situations, the amygdala has been shown to modulate “memory regions” in the medial temporal lobe (including the hippocampus and parahippocampal gyrus) (McGaugh et al. 1996; LeDoux 1996; Kilpatrick and Cahill 2003; Richter-Levin 2004; Kensinger and Corkin 2004; Phelps and LeDoux 2005; Phelps 2006; Peper et al. 2006; Depue et al. 2007) and to interact with the prefrontal cortex (PFC) (Kilpatrick and Cahill 2003; Delgado et al. 2008; van Stegeren et al. 2010). Merely presenting affective words along with emotionally arousing pictures has been shown to activate the ventrolateral PFC and to deactivate the amygdala (Lieberman et al. 2007). Smith et al. (2006) have shown that the retrieval of emotionally valenced contextual information is associated with enhanced connectivity from the hippocampus to the amygdala. On the other hand, during the encoding of emotional words, the medial frontal gyrus (MFG) (Crosson et al. 2002) and the inferior frontal gyrus (IFG) (Kensinger and Corkin 2004) were found to be activated. The MFG (Wright et al. 2002) and the IFG (Bellace et al. 2005) were also found to be activated during the encoding of emotional pictures.

Sperling et al. (2001) investigated neural correlates for the associative learning of names and faces. In addition to the hippocampus and parahippocampal gyrus, they found that the PFCs, particularly the IFG and MFG, were activated as well as the caudate, fusiform, and superior parietal cortices for encoding novel as compared with repeated face and name pairs. Several other studies have reported activation of the inferior frontal cortices during various word or picture associative encoding tasks (Dolan and Fletcher 1997; Epstein et al. 2002; Strange et al. 2005).

From the studies mentioned above, we expect to observe activation of both the PFCs and the amygdala during the association of verbal with visual emotional information. Based on the above, we hypothesize that learning while associating words with visual emotional stimuli involves top-down

processing from the PFC to primary emotional centers such as the amygdala. Thus, in contrast to the case of emotional learning, in which the amygdala influences the PFC unidirectionally (Kilpatrick and Cahill 2003; Delgado et al. 2008; van Stegeren et al. 2010), and emotion regulation, in which the PFC can downregulate emotional centers (Ochsner et al. 2004; Banks et al. 2007), we expect that a reciprocal influence of both cognitive and emotional centers is involved in associative cognitive-emotional learning. Our hypothesis is backed up by theoretical framework studies. In their review of emotional learning, LaBar and Cabeza (2006) proposed an emotional learning model that explicitly includes the bilateral connections between the amygdala and both the ventral PFC and the dorsal PFC. Furthermore, in his review of models for functional networks in the brain based on neuroimaging studies, Friston concluded that top-down influences in these networks are prevalent (Friston 2002) and extended this conclusion to include learning (Friston 2005).

In order to investigate emotional associative learning of verbal and visual information, we created a word-picture associative learning task (ALT). Subjects with healthy emotional cognition had to learn associations between words and pictures (that were either neutral or emotionally arousing) during functional magnetic resonance imaging (fMRI). Because language is arbitrary, that is, there are few clues about the meanings of words from their sounds (apart from onomatopoeic words such as crack, sizzle, or moo, Karmiloff and Karmiloff-Smith 2002), the words in the ALT were arbitrary and were matched by valence to the picture. In this way, our aim was to evoke the real learning of words by adult subjects. To our knowledge, no previous studies have investigated the directional connectivity that underlies the process of learning while making associations between verbal and visual emotional stimuli.

We carried out analyses of the effective connectivity between the IFG, the MFG, which both belong to the PFC and the amygdala. The selection of these regions to construct our models is supported by anatomical studies in rhesus monkey of connections from the amygdala to the MFG (Brodmann areas [BA] 24, 25, and 32), from the amygdala to the IFG (BA 45 and 46) (Amaral and Price 1984) and from the IFG to the MFG (Vogt and Pandya 1987). Human functional studies have also investigated the connections among these areas involved in various emotional memory tasks (Dolcos et al. 2004; Summerfield et al. 2006; Depue et al. 2007).

## Materials and Methods

### Subjects

This research was approved by the Medical Ethical Committee of the University Medical Center Groningen. Twenty students, 3 males and 17 females, participated in this study. The subjects were chosen from a sample of 493 university students using the Bermond-Vorst Alexithymia Questionnaire (Vorst and Bermond 2001). In order to exclude subjects with verbal emotional processing difficulties, the participants were selected from the group that obtained good scores in the lowest 25% on the verbalizing subscale, which measures difficulties with verbalizing emotions.

### Stimuli and Task

The subjects in our study performed a word-picture ALT during an fMRI scan. Positive, negative, and neutral emotional pictures (international affective picture system [IAPS]) were presented together

with a word from the Hermans and De Houwer database (Hermans and De Houwer 1994) (see Supplementary Fig. S2 and Tables S1 and S2). More information on the choice of words and pictures is given in the Supplementary Material. The word valence was matched to the picture valence in the sense that a negative picture (e.g., a snake) was paired with a word with a negative meaning (e.g., cancer). However, the semantics of the word was arbitrary, that is, it was not directly associated with the target IAPS picture. The pictures randomly included people, animals, houses, and landscapes. The subjects were instructed to decide whether the picture and word were associated (by pressing a button during the scanning procedure) and to memorize the combination. No instructions were given on how to associate the picture and the word. In this way, we aimed to stimulate the subjects to engage both their cognitive and emotional processes while learning new material. The quantity of material correctly remembered by the subjects was tested afterward.

### Experimental Procedure

During fMRI scanning, an emotional picture and a word were displayed for 3 s (Fig. S2). The subject was instructed to decide whether the word and picture fitted together and to remember them. During a period of 2–8 s (jittered), a fixation point was presented on the screen. There were 72 presentations of different picture-word combinations (24 for each category).

A memory test was performed after the fMRI session outside the scanner, thus within a 2 h after the learning period. The subject was presented in random order with the same pictures that had been shown in the scanner. Below the picture, 3 words were given (in random order): 1) the word that was paired with the picture (the correct answer), 2) a word semantically related to the paired word in the scanner, and 3) an unrelated word. The subject was asked to choose the right answer by pressing 1, 2, or 3.

### fMRI Data Acquisition

The images were acquired using a 3-T Philips Intera MRI scanner (Philips, Best, The Netherlands). The standard 6-channel SENSE head coil was used to acquire whole-brain echo-planar functional images (EPIs). Thirty-nine axial slices were acquired with the following parameters: time repetition (TR) 2000 ms, echo time (TE) 28 ms, flip angle 70°, SENSE factor 2; field of view (FOV) 224 mm, matrix 64 × 64, slice thickness 3.5 mm with no slice gap, and yielding voxels of 3.5 × 3.5 × 3.5 mm in size. In addition,  $T_1$ -weighted anatomical images were acquired: 3D/FFE/CLEAR to coregister and normalize functional data (TR = 25 ms, TE = 4.6 ms, flip angle = 30°, FOV = 256 mm, matrix 256 × 256 mm, slice thickness 1.0 mm).

### Preprocessing and First-Level Data Analysis

The collected magnetic resonance data in the form of 4D volumes were first converted to 3D files using the MRIcro software and then processed using the statistical parametric mapping program SPM8 ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)). Because the obtained EPI data were interleaved, in order to prepare the data for the dynamic causal modeling (DCM) analysis, the functional images were corrected for slice-timing acquisition as a part of the preprocessing procedure. The images were then realigned to the first functional image. The  $T_1$ -weighted images were coregistered to the mean EPI image. Low-frequency signal drift was corrected for by applying a high-pass temporal filter with a cutoff of 250 s. The coregistered data were subsequently normalized onto the Montreal Neurological Institute template, and the resulting normalization parameters were applied to all the EPI images. The functional data were spatially smoothed using a 6-mm isotropic Gaussian Kernel before the statistical analysis.

Statistical analysis at the first level was performed using a general linear model (GLM) with random-effects (RFX) analysis on the group level. The regressors for the experimental conditions were convolved by a canonical hemodynamic response function in order to estimate, voxel by voxel, the parameters denoting the unique (linear) contribution of each condition to the measured blood oxygen level-dependent (BOLD) signal in each subject. In order to identify those areas involved



in emotional processing of the task, the contrast was performed for each subject, using a *t*-test to compare the activation for the positive (P) + negative (N) emotional condition versus the neutral (n) condition. The results were used as input to the RFX for the group inferences. In order to investigate the process of associative learning, we analyzed both successfully and unsuccessfully memorized trials. The RFX maxima from the contrast served as the basis for time-course extraction for the DCM analysis.

### Effective Connectivity

We used the DCM option in SPM8 (Friston et al. 2003) to evaluate the effective connectivity between the MFG, the IFG, and the Amy. The principle of the DCM approach to effective connectivity using fMRI data was first introduced by Friston (Friston et al. 2003) and implements a predefined model of how the observed data are caused (Friston 2009). DCM is based on bilinear differential equations approximating the dynamics of interacting neuronal populations. These neuronal state equations are combined with a forward model, the hemodynamic balloon model (Buxton et al. 1998; Stephan et al. 2007), which links neuronal population activity to the predicted regional BOLD response by considering how neuronal activity leads to regional vasodilation, blood flow, changes in blood volume, and deoxyhemoglobin content. By comparing the BOLD response predicted by DCM with the measured BOLD signal, the parameters of the model are adjusted by means of iterative Bayesian estimation such that a free energy bound on the model evidence is optimized. We note that this Bayesian procedure does not simply perfect the model fit but optimizes the balance between the model fit and model complexity; this is an important feature of DCM that prevents overfitting. As a result of this iterative computation, the following 3 types of coefficients are calculated: 1) the strength of the connections between 2 regions (referred to as directional connectivities and denoted by coefficients A), 2) the strength of modulation of the connection by a certain external input or condition (known as modulatory effects and denoted by coefficients B), and 3) the direct influences of the external input or condition on the region (known as driving inputs and denoted by coefficients C). By selecting different combinations of directional connectivities, modulatory effects, and direct inputs, different DCMs can be produced for the same set of regions.

### Selection of Volumes of Interest

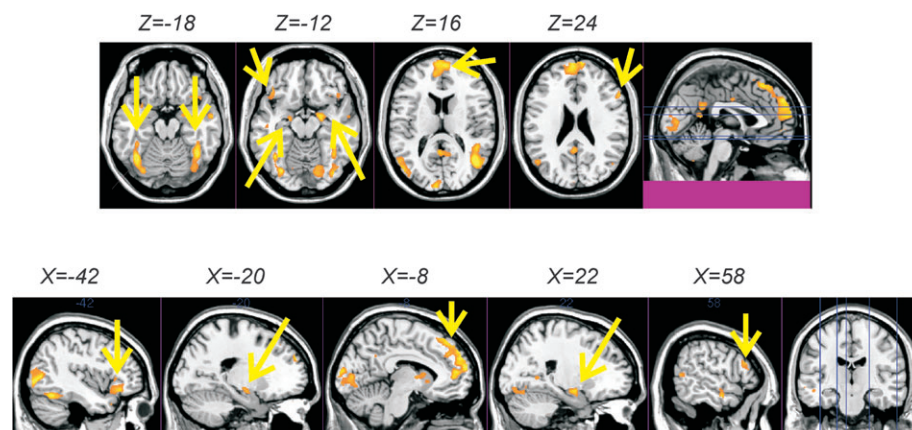
The time courses were extracted from the volumes of interest (VOI) for each subject, which were defined as follows. First, the RFX maxima belonging to a given anatomical region were chosen by locating the maximum of the activation within the region defined by overlapping the RFX results for (P + N vs. n) contrast ( $P < 0.001$ , uncorrected) and

the “TD labels” (for the MFG and IFG) and “aal” (for amygdala) maps from *wfu\_pickatlas* (Tzourio-Mazoyer et al. 2002; Maldjian et al. 2003, 2004). We chose this contrast in order to bias the selection of voxels toward those that are engaged in emotional memorizing. The center of the VOI for each subject was then defined as the maximum activation (P + N vs. n contrast,  $P < 0.05$ , uncorrected) in the given region, close to the RFX maximum (cutoff at 16 mm) and still belonging to the same anatomical region (visual inspection). Finally, 4-mm spheres were drawn around the center defined above, and time series of the activated voxels within the sphere were extracted while their first principal component (*y*) was simultaneously calculated. The first principal component was used for further connectivity analysis.

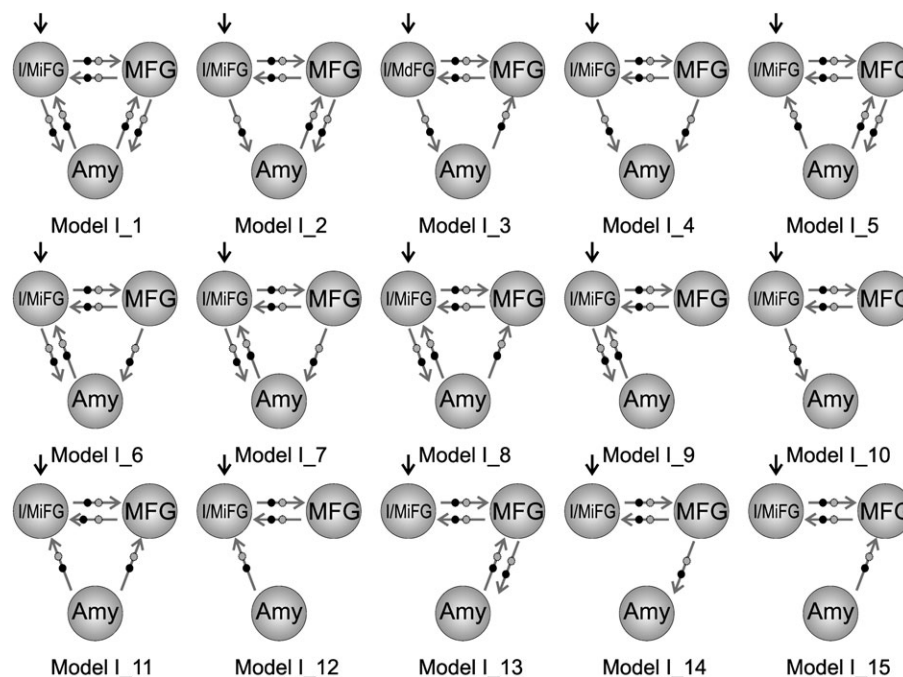
### Model Space

We examined the interactions of the amygdala with the MFG, which is sensitive to tasks involving emotions, error monitoring, and self-related processing (Amodio and Frith 2006; Olsson and Ochsner 2008). We also studied the interactions of the amygdala with the IFG, which has been implied in emotion regulation (Ochsner et al. 2004; Banks et al. 2007), working memory and strategy selection (Fairhall and Ishai 2007), and particularly language tasks (Lieberman et al. 2007; Heim et al. 2009). More specifically, the left IFG is crucial for verbalizing ability (Dronkers et al. 2007) and is thought to be involved in the selection of task-relevant information (emotional connotation as target information from specific competing semantic alternatives) (Heim et al. 2009). We based our models on anatomical studies that have revealed bilateral connections between the regions of interest (see Introduction).

We created a model space starting with 15 different models (see Fig. 2). We used a different combination of effective connectivities to test whether bottom-up (from the amygdala to the prefrontal areas, i.e., the IFG and the MFG) or top-down (from the prefrontal areas to the amygdala) connections are dominant. All the existing connectivities had modulatory effects for both P and N emotions. Being unclear from the literature, it was necessary to estimate which region first received input (positive—P and negative—N conditions) using a procedure similar to that described by Ethofer et al. (2006)). In that study, full models (consisting of all the possible effective connectivities and modulatory effects) were created using all the possible input combinations (see Fig. S1). Consequently, we created a model space consisting of all the possible inputs to the 15 models explained above. Thus, our model space consisted of  $7 \times 15$  models. This well-justified (Stephan et al. 2010) exploratory step was necessary in order to determine whether top-down or bottom-up influences of emotions are prevalent in the connectivity network because the stimulus enters the model at the input region(s) and then propagates through the model.



**Figure 1.** Results of conventional analysis. The contrast indicates ALT emotional > neutral (RFX *t*-test) for 19 subjects, revealing activation of the bilateral IFG/MidFG, MFG, and Amy ( $P < 0.005$ ,  $T > 3.1$ ). Top panel axial view: the *z* coordinate is indicated above each slice, and arrows indicate (from left to right) the bilateral fusiform gyrus, bilateral amygdala and left IFG/MidFG, MFG, right IFG/MidFG; the sagittal view on the right illustrates the positions of the axial slices. Bottom panel, sagittal view: the *x* coordinate is indicated above each slice, and arrows indicate (from left to right) the left IFG/MidFG, left amygdala, MFG, right amygdala, right IFG/MidFG; the coronal view on the right illustrates the positions of the sagittal slices.



**Figure 2.** DCM comparison—illustration of models of effective connectivity during an ALT. Input consisting of positive and negative conditions is for example provided to the IFG/ MidFG (I/MiFG in figure). The models I\_4, I\_10 and I\_14 have only top-down connections (top down), the bottom-up models are I\_11, I\_12 and I\_15, and the rest are combined (having both top-down and bottom-up connections). Gray dots illustrate modulatory effects by negative stimuli, and black dots illustrate modulatory effects by positive stimuli. The inputs were varied systematically for all models (7 variations are depicted in Fig. S1).

The models were then compared using Bayesian model selection (BMS) (Penny et al. 2004; Stephan et al. 2007, 2009) (see below) on the group level. We estimated the connectivity parameters using Bayesian model averaging (BMA) in order to compute the average model parameters from the winning families (see below).

We also calculated the connectivity coefficients and the modulatory effects, which were estimated in a classical way by calculating the mean value and statistical significance for the group using the SPSS program (version 16.0) and a 2-tailed *t*-test on the best model (see Supplementary Material). Those surviving the  $P < 0.05$  significance level after false discovery rate (FDR) correction were reported.

#### BMS and BMA

The models were compared on the group level using the BMS approach (Penny et al. 2004) combined with the RFX Bayesian method described by Stephan et al. (2009). In short, a probability density is estimated on the models themselves. This new variational Bayes method is based on treating the model as a random variable and estimating the parameters of a Dirichlet distribution that describes the probabilities for all models considered. As a consequence, it is possible to estimate how likely it is that a specific model generated the data of a randomly chosen subject, as well as the exceedance probability of one model being more likely than any other model. Families of models were compared in a similar manner. Three families were created: models with bottom-up connections—the bottom up family, models with top-down connections—the top-down family, and a family with both top-down and bottom-up connectivities.

BMA computes parameters within chosen group of models (e.g., family) and as such summarizes group-specific coupling parameters (Penny et al. 2010). This method is convenient when many models are compared and when there is not an obvious single winning model. In short, the posterior densities of the parameters were calculated across all the subjects and across all the selected models (in this case for models belonging to a certain family). More weight was given to the models with higher posterior probability according to Bayes' rule. The posterior distributions were calculated by drawing samples from a multinomial distribution of posterior beliefs for given models within subjects using a Gibbs sampling approach (Penny et al. 2010). Finally,

posterior means and exceedance probabilities (that the parameter is larger than zero) were obtained.

## Results

### Memory Task Results

Nineteen out of 20 subjects performed uniformly well in the memory test, with a mean accuracy of  $93\% \pm 13\%$  (mean  $\pm$  standard deviation,  $n = 20$ ). One subject performed poorly, scoring 42% correct, and was excluded from further connectivity analysis. We found an effect of valence  $F_{2,18} = 2.584$ ,  $P = 0.0445$  (one-tailed because we expected to find increased memory performance for emotional material compared with nonemotional material). Accuracies for the various trials are given in Tables S3 and S3-1. The planned contrast (Table S4) revealed a difference in the accuracy of performance between emotional and neutral trials ( $P = 0.038$ ,  $n = 19$ ). The same analysis was repeated for 2 subgroups of subjects that had significant activation in all 3 ROIs in the left and in the right hemisphere. The results were similar (details are in Supplementary Tables S3-1 and S4-1)—subgroup that was encountered for DMCs in left hemisphere had an effect of valence  $F_{2,10} = 3.198$ ,  $P = 0.031$  (one-tailed) and subgroup right  $F_{2,12} = 3.399$ ,  $P = 0.025$  (one-tailed).

### Relatedness of Stimuli

The subjects judged that 45% of the positive word and picture stimuli did not match (for details, see Supplementary Table S2-1 and Supplementary Material). Similarly, 40% of the negative stimuli did not match, whereas the corresponding fraction for neutral stimuli was 93%. The subgroup consisting of subjects used in the DCM analysis had a similar response pattern with

46% of positive, 41% of negative, and 92% of neutral stimuli not matching.

We investigated further how the above relatedness affected the memory test results. Repeated-measures analysis of variance (ANOVA) revealed that emotions have a significant effect on the subgroups of matching and not matching trials ( $F_{2,32} = 5.295$ ,  $P = 0.010$  and  $F_{2,32} = 4.859$ ,  $P = 0.014$ ). The planned contrasts revealed a difference in the memory accuracy between emotional and neutral trials ( $F_{1,16} = 9.873$ ,  $P = 0.006$  for matching and  $F_{1,16} = 14.306$ ,  $P = 0.002$  for nonmatching responses). Thus, there is an effect of emotion that is independent of relatedness. In addition, factorial ANOVA revealed a tendency toward significant interaction between emotions and relatedness with  $F_{1,10} = 3.091$ ,  $P = 0.068$  (planned contrast between emotions and neutral  $F_{2,20} = 10.8$ ,  $P = 0.008$ ).

### Conventional Analysis and VOI Selection

Figure 1 and Table S5 present the group activation revealed by conventional voxel-based analysis during the ALT. RFX GLM analysis of the emotional versus neutral condition ( $P < 0.05$ , FDR) revealed activation of the bilateral Amy, IFG, and MFG (Fig. 1, top panel). We also observed increased activation in the middle frontal gyrus (MidFG), fusiform gyrus (visual processing area), middle temporal gyrus, superior temporal gyrus, superior frontal gyrus, caudate and posterior cingulate, and decreased activation in the inferior parietal lobule. Because the highest activated voxel in the IFG is very close to the MidFG, we refer to the VOI for the IFG as the IFG/MidFG.

The results of the conventional RFX analysis of this contrast are given in Figure 1. Table 1 lists guiding coordinates on the group level for VOI selection. Individual VOIs were extracted from the first-level analysis (emotional > neutral,  $P < 0.05$ ) in the proximity of these coordinates as long as they fulfilled 3 conditions: 1) the sphere belongs to a particular area (visually inspected for each subject on its normalized anatomy), 2) the centers of the VOIs are as close as possible to the highest activated voxel of that area for that particular subject, and 3) the centers of the VOIs are within a 16-mm radius of the RFX centers listed in Table 1. We found significant activation in the right hemisphere for all 3 areas in 13 subjects and in the left hemisphere in 11 subjects.

In addition, the RFX analysis with 9 conditions (Table S5-1) including the subjects' matching responses suggests that the VOIs selected for DCM analysis include emotional activation independent of relatedness of stimuli.

### Effective Connectivity

We investigated the effective connectivity between the MFG, IFG/MidFG, and amygdala for both the left hemisphere ( $n = 11$ )

and the right hemisphere ( $n = 13$ ), modeling the extracted time courses using DCM.

Subsequently, we aimed to establish the directionality of the connections between the PFC and the amygdala. The 15 plausible models were created such that different models had different combinations of effective connectivities. The input was varied systematically for all 15 models. The modulatory effects from positive and negative emotional stimuli were attributed to all the connections. The models were then divided into 3 groups as described in the Materials and Methods section.

The group BMS revealed quite convincingly that for both hemispheres, the model with the IFG/MidFG as the input area had the highest exceedance probability (Fig. 3*a,b*). Figure 3*c* and Table S6 show the posterior family probabilities from the RFX analysis. We are unable to state with great confidence whether the connections between regions are purely top-down or combined (the exceeding probabilities are 35% and 60% respectively in the left hemisphere and 46% and 53% in the right hemisphere). However, we can conclude with full confidence that purely bottom-up connections are extremely unlikely; the exceeding probabilities are ~1% for the bottom-up family in both hemispheres.

### Effective Connectivities and Modulatory Effects

#### Standard *t*-Test

The results of the BMS (see Table S7 and Fig. 3*a,b* for model selection) resulted in competition between models I\_4 (exceedance probability 24% in the left hemisphere and 29% in the right), I\_10 (10% in the left hemisphere and 17% in the right), and I\_1 (15% in the left hemisphere and 12% in the right) for both hemispheres. We can say with moderate confidence that I\_4 is the best model, consisting of reciprocal effective connectivities between the IFG/MidFG and MFG and top-down connectivities from the IFG/MidFG and MFG toward the amygdala and all the modulatory effects. The mean values and statistical significance are reported in Table S8. In the left hemisphere, all the effective connectivities are significantly different from zero. In the right hemisphere, the connectivities from the IFG/MidFG and the MFG to the amygdala survive the threshold. All the mean values are positive. In the left hemisphere, positive stimuli increase the top-down connectivities, whereas negative stimuli increase the connectivity from the IFG/MidFG to the amygdala. In the right hemisphere, both conditions increase the top-down connectivities. Moreover, the negative condition increases the connectivity from the IFG/MidFG to the MFG (86.5%,  $P = 0.015$ ; Table S8).

#### BMA Results

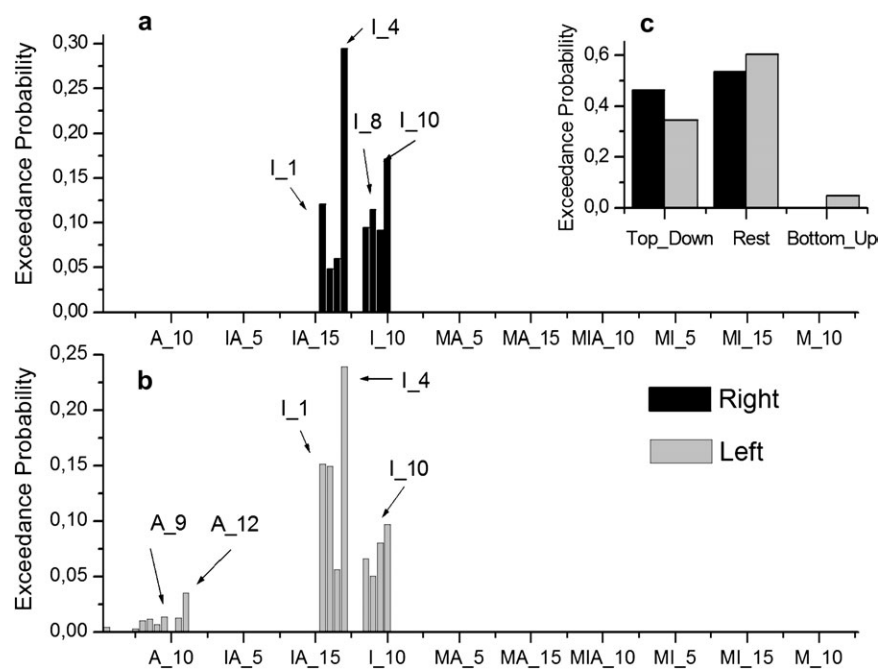
Given that the exceeding probabilities for models I\_4, I\_1 and I\_10 were comparable and that the exceeding probabilities for most of the other models were only 2 to 3 times smaller (not 10 or 100 times as for the input selection), the BMA method is appropriate in order to look for the parameter estimates. Therefore, the effective connectivity and modulatory effect parameters were calculated for the winning families using BMA. Table 2 summarizes the results. The threshold was set to 90%, although we also consider a threshold of >85% as a statistical trend. In the left hemisphere, the intrinsic connectivities from the IFG/MidFG and those from the amygdala to the IFG/MidFG have parameters whose sample distributions are in 90% of cases

**Table 1**  
Results of Conventional analysis

EMO vs. NEU	BA	x	y	z	z	k
LAMY		-20	-6	-14	3.5	19
RAMY		22	-4	-12	4.4	96
LMFG	BA10	-8	64	18	5.0	757
RMFG	BA10	6	62	14	4.5	278
LIFG/MidFG	BA47	-42	30	-12	4.2	415
RIFG/MidFG	BA45	58	26	24	3.9	103

Note: RFX, emotional > neutral. The columns list the chosen centers of the VOI sphere close to the highest activated voxel within the region of interest, the Brodmann area, the Montreal Neurological Institute coordinates, and the z score at that point.





**Figure 3.** Results of BMS. Exceedance probabilities for (a) the right hemisphere, (b) the left hemisphere, and (c) 3 model families.

larger than zero. Furthermore, negative stimuli increase the connectivity from the IFG/MidFG to the amygdala (in 87% of cases), and the connectivity from the amygdala to the MFG is greater than zero in 87% of samples. This can be considered as a statistical trend. In the right hemisphere, the outgoing connections from the IFG/MidFG survive. Furthermore, negative emotions influence the connectivities from the IFG/MidFG to the MFG in the same manner as in the left hemisphere. The difference between hemispheres is in the extent of influence (33% in the left and 53% in the right hemisphere). We can say with greatest certainty that negative emotions increase the connectivity from the IFG/MidFG to the MFG in the right hemisphere. There is a statistical trend toward significance for the increase in the connectivity from the IFG/MidFG to the amygdala due to positive stimuli.

The calculated coupling parameters were correlated with the results of the memory test (the accuracies for emotional material and the total accuracy score). We found no significant correlation. This might be due to the fact that the accuracy was rather high (see above) and spanned a narrow range.

## Discussion

In this study, we investigated the effective connectivity in the frontoamygdalar circuits for a type of emotional learning that involves the pairing of emotional words and pictures. This verbal-visual associative learning represents a primary mechanism of language development and, when combined with emotional context, is especially important for the acquisition of emotional knowledge and emotional verbalizing skills, which are principles of emotion regulation in daily life (Eisenberg et al. 2005). By comparing the families of models, we observed a bidirectional information flow. However, our task had a strong top-down component, as participants were instructed to pair emotional words and pictures, which presumably triggered an active approach and the use of strategies. We found that

increases in the connectivity between frontal areas of the brain and the amygdala due to emotional (particularly negative) stimuli may underlie emotional associative learning. This effect was particularly apparent for negative stimuli within the PFC in both hemispheres.

## Emotional Learning

During fMRI scanning, the subjects performed an emotional memorizing task in which they had to engage a cognitive strategy to memorize emotional pictures and words. As expected, we observed that emotions had a significant effect on the memory process such that pairs of emotional words and pictures were better memorized than neutral combinations. This is in line with studies showing that both words and pictures having an emotional content or context are better memorized than neutral material (Bradley et al. 1992; Hamann et al. 1999; Brierley et al. 2007). Even though our experimental design was unbalanced with respect to matching and non-matching stimuli for different valence, when only matching or only nonmatching stimuli were observed, emotions had a significant effect on the memory process and on brain activation of the selected ROIs.

Summarizing the results of the model family comparison and the BMA, we can conclude that there is a bidirectional flow of information between the PFC and the amygdala during the association of emotional verbal and visual stimuli. The BMA results show clearly that the top-down (from the PFC regions of the IFG/MidFG and MFG toward the amygdala) components are stronger (the largest coefficient of intrinsic connectivity is 0.2, as compared with 0.1 for the bottom-up component). However, both the model family comparison and the BMA suggest that the bottom-up (from the amygdala toward the PFC regions) components (especially in the left hemisphere) are nonnegligible, illustrating that there is interplay between the PFC and amygdala during associative emotional learning. Our findings that the IFG/MidFG receives the input first suggest

**Table 2**  
Results of BMA

Connection	Coefficient mean	Exceedance probability (%)	Percent of modulatory influence
<b>Left</b>			
MFG to Amy	0.047	77.5	
MFG to IFG/MidFG	0.071	82.2	
<b>Amy to MFG</b>	<b>0.062</b>	<b>85.4</b>	
<b>Amy to IFG/MidFG</b>	<b>0.117</b>	<b>96.2</b>	
<b>IFG/MidFG to MFG</b>	<b>0.214</b>	<b>100</b>	
<b>IFG/MidFG to Amy</b>	<b>0.222</b>	<b>100</b>	
P MFG to Amy	0.005	53.6	
P MFG to IFG/MidFG	0.012	56.3	
P Amy to MFG	0.001	50.3	
P Amy to IFG/MidFG	0.022	63.4	
P IFG/MidFG to MFG	0.022	63.2	
<b>P IFG/MidFG to Amy</b>	<b>0.047</b>	<b>75.3</b>	21.2
N MFG to Amy	0.010	55.6	
N MFG to IFG/MidFG	0.017	58.7	
N Amy to MFG	0.015	59.9	
N Amy to IFG/MidFG	0.035	70.7	
<b>N IFG/MidFG to MFG</b>	<b>0.070</b>	<b>86.1</b>	33
<b>N IFG/MidFG to Amy</b>	<b>0.078</b>	<b>87.7</b>	<b>35</b>
<b>Right</b>			
MFG to Amy	0.036	76.2	
MFG to IFG/MidFG	0.021	61.0	
Amy to MFG	0.041	76.9	
Amy to IFG/MidFG	0.011	56.5	
<b>IFG/MidFG to MFG</b>	<b>0.217</b>	<b>100</b>	
<b>IFG/MidFG to Amy</b>	<b>0.236</b>	<b>100</b>	
P MFG to Amy	0.005	53.2	
P MFG to IFG/MidFG	-0.001	49.4	
P Amy to MFG	-0.003	48.4	
P Amy to IFG/MidFG	-0.002	48.8	
P IFG/MidFG to MFG	0.001	50.9	
<b>P IFG/MidFG to Amy</b>	<b>0.077</b>	<b>88.9</b>	32.8
N MFG to Amy	0.007	55.2	
N MFG to IFG/MidFG	0.016	59.4	
N Amy to MFG	0.013	58.8	
N Amy to IFG/MidFG	0.014	58.6	
<b>N IFG/MidFG to MFG</b>	<b>0.115</b>	<b>97.8</b>	<b>52.5</b>
<b>N IFG/MidFG to Amy</b>	<b>0.062</b>	<b>84.2</b>	<b>26.4</b>

Note: Coefficients for effective connectivity and modulatory effects statistically determined by BMA. The coefficients with exceeding probabilities exceeding 85% are given in bold.

that in the case of associative learning of emotional words and pictures, the amygdala is not only involved in rapid processing and initial detection but also in more elaborate social judgment and in the recognition of emotions. This is in accordance with studies investigating fearful faces (Pessoa et al. 2006; Tsuchiya et al. 2009), in which it was found that the amygdala is not involved in rapid preattentive detection but rather in the conscious detection of fear and in the modulation of social judgments of fear. Our results indicate that during a cognitive emotional task that demands adopting some strategy for learning, the frontal cortex interacts with the amygdala or even takes the lead by first receiving the input, thus providing additional evidence for the critical role of the PFC in the formation of new associations (Sperling et al. 2001). We suggest that while the PFC orchestrates error monitoring and the proper memorizing and associating of information, the amygdala boosts the emotional relevance of the information. This significant finding that the PFC seems to “call upon” the amygdala and that it engages in bidirectional interactions is consistent with a study of Roozendaal et al. (2009) in which they demonstrated that bidirectional interactions take place between the MFC and the basolateral amygdala in rats during memory consolidation.

The activation of the amygdala is consistent with the interpretation that emotional arousal has occurred (Kilpatrick

and Cahill 2003; Kensinger and Corkin 2004). It is therefore unlikely that the weaker influence of the amygdala on the prefrontal areas is due to a failure of the task to trigger emotional brain systems. Indeed, the IAPS pictures that we used have frequently been shown to robustly activate the amygdala and related structures (Liberzon et al. 2003; Britton et al. 2006).

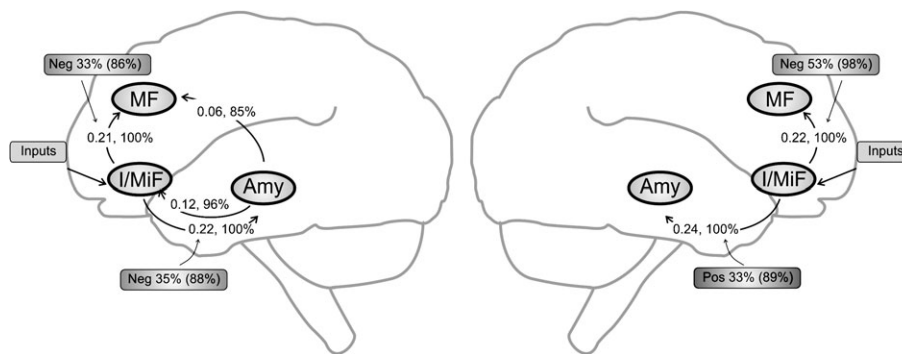
The positive coefficients of the connectivity from the IFG/MidFG to the amygdala indicate that an increase in activation of the IFG/MidFG is accompanied by an increase in activation of the amygdala. This differs from the case of emotional reappraisal, where the right IFG/MidFG has been implicated in downregulating the amygdala (Ochsner et al. 2004). Indeed, our task did not involve reappraising emotions but rather attending to them and engaging cognitive strategies to learn emotional material, which might explain the difference in the direction and lateralization of the connection effect.

Animal anatomical studies support our models. Strong connections between the medial cortical surfaces and the amygdala that have been traced in marmoset monkey (Roberts et al. 2007), rhesus monkey (Amaral and Price 1984), and other primates (Barbas 2000) corroborate our models in which the MFC has a bilateral effective influence on the amygdala. The lateral cortex in marmoset monkey, resembling BA 12/45 of macaques, was found to have extensive connections to the limbic regions (Roberts et al. 2007). The heaviest projections from the amygdala were found to lead to the medial prefrontal and orbitofrontal cortex in macaque monkey, and lighter projections to lateral regions including BA 45/46 IFG/MidFG were identified (Amaral and Price 1984). Caudal medial cortices—also known as limbic PFCs—have been found to receive input from the amygdala, associated with emotional memory, in cats, rats, and monkeys (Barbas 2000). Our findings suggest that direct communication between the IFG/MidFG and the amygdala occurs during emotional associative learning, despite the weaker anatomical connections from the lateral cortices to the amygdala. This is evident from the connectivity strengths among the 2 areas (see Fig. 4): the unilateral effective connectivity from the IFG/MidFG to the amygdala is  $A = 0.2$  (for both hemispheres), whereas the route via the MFG has a lower connectivity strength and significance (below the trend threshold).

It has previously been shown that the PFC connections are largely reciprocal (Price 2003) and highly interconnected, which is also in line with our model (Barbas 2000). In primates, the PFCs underlie the synthesis of cognition, memory, and emotion. The finding that they are strongly interconnected suggests that they participate in concert in central executive functions. In line with the above, our findings suggest that the inferior frontal cortex acts upon the medial frontal cortex to process and to coordinate associative emotional memory. This effect is particularly enhanced under negative emotional stimuli.

Another notable finding of our study is that negative emotional stimuli tends to enhance the connectivity between the left IFG/MidFG and the amygdala, while positive stimuli enhance the connectivities from the right IFG/MidFG and the amygdala. This is in agreement with the study of Kilpatrick and Cahill (2003), who used structural equation modeling to demonstrate an increased efferent influence of the right hemisphere amygdala on the ipsilateral parahippocampal gyrus and the IFG in men during the encoding of emotional (as





**Figure 4.** Results of BMA. Effective connectivity coefficients that exceed the threshold level of  $P = 90\%$  (solid arrows) and their exceedance probability are denoted. The modulatory effects for positive (P) and negative (N) stimuli are presented with the percentage of influence on the effective connectivity and the exceedance probability (in brackets). The percentage of influence was defined as  $\% = \frac{M_B}{M_A} \times 100$ . Here,  $M_A$  is the mean of the directional connectivity, and  $M_B$  is the mean of the modulatory effect coefficient.

compared with neutral) film clips. Partially consistent with our observation, Buchanan et al. (2001) found that patients with lesions of the left amygdala lack the emotional enhancement of memory that patients with damage only to the right amygdala still exhibit. The bilaterally enhanced connectivity in our study is most probably due to the different nature of the task that we used, which comprised the processing of both words and pictures. Kelley et al. (1998) suggested that the PFCs show hemispheric specialization based on the content of the stimuli, identifying left prefrontal activation during word encoding, right prefrontal activation during face encoding, and bilateral prefrontal activation for “nameable objects.” The task used by Kilpatrick and Cahill did not require the explicit encoding of emotion (the subjects were not told that their memory would be tested) or the involvement of emotional verbal systems. Our findings of bilateral involvement are consistent with those of Sperling et al. (2001), who observed bilateral activation in the prefrontal regions during the encoding of face and name pairs.

### Limitations

Notably, our conclusions are based on the use of one particular model—a dynamical causal model with bilinear correlations. This model estimates the directional connectivities together with the modular effects on these connectivities produced by various inputs on the neural level. The effective directional connectivities are estimated as the degree of change of activation of the observed area induced by activation of another area. Other models have already been reported (such as the nonlinear dynamic causal model, Stephan et al. 2008, which includes the possibility that a third area influences connections between the first 2 areas) that might provide more detailed insight into the various interactions between areas. We may also question to what degree a change of activation in one area induces a change of activation in the observed area (modeling so-called change detectors). Nevertheless, our bilinear model serves as a simple first step toward revealing the interactions among brain areas during this strategic cognitive task. The main advantage of our approach is that it allows the exploration of interactions among predefined and theoretically relevant brain areas.

Our main concern in this study was to investigate the learning of emotional association with emphasis on the emotion. Therefore, our task was created to pinpoint the processes

involved in the associative learning of emotional material as opposed to neutral material. In further investigation, one might wish to distinguish the process of learning from perception of these word-picture pairs. Our study cannot disentangle perception and encoding because the results of the memory tests were very high. However, activation was measured during the learning phase, and the fact that memory was good evidences that the emotional learning took place during the scans. For the same reason, the subjects were not instructed to adopt any particular cognitive strategy, but were allowed to choose for themselves the most suitable manner of deciding whether or not the word and picture fitted together. In this way, we ensured that the subjects engaged in a cognitive strategy while learning the emotional material. Again, the high scores on the memory test and the instruction to press a button to indicate whether or not the word and picture fitted together were merely control methods to ensure that the subjects concentrated on the task and to witness that they performed the task correctly. We carefully considered the effect of relatedness on the analyses. We would like to emphasize that our experiment was not designed to investigate the relatedness of the stimuli. The judgment regarding relatedness was only used to evoke cognitive processes (as described above), in particular associative processing. The imbalance in the relatedness of emotional and neutral stimuli did not affect our connectivity analysis, which was confined to emotional stimuli (among which the distribution was balanced). The result that emotions affect memory accuracy for both matching and nonmatching stimuli suggests an independent effect of emotion. In addition, the fMRI results for the contrast emotional versus neutral stimuli in which only nonrelated stimuli were included suggest that the ROIs for the connectivity analysis are affected by emotional processing independent of relatedness.

We also emphasize that we have investigated only the network of prefrontal regions with the amygdala; we did not incorporate the hippocampal formation. We remind the reader here that our emphasis was on emotion, thus we investigated regions with respect to the emotion versus neutral contrast. Both the hippocampus and the PHG have been implicated in the detection of novelty (Tulving et al. 1996); because both the emotional and neutral stimuli were novel to the subjects, it is of no surprise that neither was significantly increased in the emotional versus neutral contrast.

## Conclusion and Future Perspectives

In conclusion, the results of our effective connectivity analyses are consistent with the hypothesis that the associative learning of emotional verbal and visual information in humans is mediated by bidirectional information flow from the frontal areas to the amygdala. Moreover, emotional stimuli tend to increase the connectivity from the frontal areas to the amygdala, which might be responsible for the emotional memory effect in this type of learning.

Our findings regarding the neural circuits that underlie complex cognitive-emotional learning processes could eventually pave the way for further investigations of emotional learning in various psychiatric disorders such as schizophrenia (Aleman and Kahn 2005), bipolar disorder (Phillips et al. 2003), and posttraumatic stress disorder (Banich et al. 2009), which are all accompanied by abnormalities in emotional perception and regulation. For example, it has been shown that patients with schizophrenia have altered patterns of connectivities while performing working memory tasks (Meyer-Lindenberg et al. 2005); the same is true for autistic patients during cognitive control (Schlösser et al. 2008). It would also be of interest to investigate the developmental trajectories of prefrontal influences on emotional learning in children, for whom it may be more difficult to verbalize emotions because the PFC is not yet fully developed.

## Supplementary Material

Supplementary materials can be found at: <http://www.cercor.oxfordjournals.org/>.

## Funding

EURYI Award from the European Science Foundation (no.044035001) to A.A.

## Notes

The authors thank B. Roozendaal, G. R. Blake, Rudie Kortekaas, and D. R. M. Langers for their comments on earlier versions of the manuscript as well as W. D. Penny, L. Nannetti, R. Renken, and C. Lanting for their comments on the analysis. *Conflict of Interest:* None declared.

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